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=> S CD95 OR FAS OR APO-1
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=> S INCREAS? OR INDUC?
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L2 10247137 INCREAS? OR INDUC?

=> S L1(S)L2
L3 22697 L1(S) L2

=> S EXPRESS?
L4 2705546 EXPRESS?

=> S L3(S)L4
L5 13033 L3(S) L4

=> S P53
L6 104368 P53

=> S L5(S)L6
L7 953 L5(S) L6

=> S CHEMOTHERAP?
L8 439321 CHEMOTHERAP?

=> S L7 AND L8
L9 112 L7 AND L8

=> DUP REM L9
PROCESSING COMPLETED FOR L9
L10 46 DUP REM L9 (66 DUPLICATES REMOVED)

=> S L10 NOT PY>1999
L11 25 L10 NOT PY>1999

=> D TI SO 1-25

L11 ANSWER 1 OF 25 MEDLINE
TI p53-mediated up-regulation of CD95 is not involved in genotoxic drug-induced apoptosis of human breast tumor cells.
SO CELL DEATH AND DIFFERENTIATION, (1999 Mar) 6 (3) 271-80.
Journal code: 9437445. ISSN: 1350-9047.

L11 ANSWER 2 OF 25 MEDLINE
TI Boswellic acids and malignant glioma: induction of apoptosis but no modulation of drug sensitivity.
SO BRITISH JOURNAL OF CANCER, (1999 May) 80 (5-6) 756-65.
Journal code: 0370635. ISSN: 0007-0920.

L11 ANSWER 3 OF 25 MEDLINE

TI Sensitization of AIDS-Kaposi's sarcoma cells to Apo-2 ligand-induced
apoptosis by actinomycin D.
SO JOURNAL OF IMMUNOLOGY, (1999 May 1) 162 (9) 5616-23.
Journal code: 2985117R. ISSN: 0022-1767.

L11 ANSWER 4 OF 25 MEDLINE
TI Distinct p53-independent apoptotic cell death signalling pathways in testicular germ cell tumour cell lines.
SO INTERNATIONAL JOURNAL OF CANCER, (1999 May 17) 81 (4) 620-8.
Journal code: 0042124. ISSN: 0020-7136.

L11 ANSWER 5 OF 25 MEDLINE
TI The CD95/CD95 ligand system is not the major effector in anticancer
drug-mediated apoptosis.
SO CELL DEATH AND DIFFERENTIATION, (1998 Sep) 5 (9) 735-42.
Journal code: 9437445. ISSN: 1350-9047.

L11 ANSWER 6 OF 25 MEDLINE
TI p53 activates the CD95 (APO-1/Fas) gene in response to DNA damage by
anticancer drugs.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Dec 7) 188 (11) 2033-45.
Journal code: 2985109R. ISSN: 0022-1007.

L11 ANSWER 7 OF 25 MEDLINE
TI Dexamethasone-mediated protection from drug cytotoxicity: association with
p21WAF1/CIP1 protein accumulation?.
SO ONCOGENE, (1998 Sep 24) 17 (12) 1567-75.
Journal code: 8711562. ISSN: 0950-9232.

L11 ANSWER 8 OF 25 MEDLINE
TI Molecular determinants of apoptosis induced by cytotoxic drugs.
SO KLINISCHE PADIATRIE, (1998 Jul-Aug) 210 (4) 148-52.
Journal code: 0326144. ISSN: 0300-8630.

L11 ANSWER 9 OF 25 MEDLINE
TI Potentiation of CD95L-induced apoptosis of human malignant glioma cells by
topotecan involves inhibition of RNA synthesis but not changes in CD95 or
CD95L protein expression.
SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1998 Sep) 286 (3)
1374-82.
Journal code: 0376362. ISSN: 0022-3565.

L11 ANSWER 10 OF 25 MEDLINE
TI CD95-mediated apoptosis: no variation in cellular sensitivity during cell
cycle progression.
SO FEBS LETTERS, (1998 Aug 7) 432 (3) 155-7.
Journal code: 0155157. ISSN: 0014-5793.

L11 ANSWER 11 OF 25 MEDLINE
TI Retinoic acids induce growth inhibition and apoptosis in adult T-cell leukemia (ATL) cell lines.
SO LEUKEMIA RESEARCH, (1998 Jul) 22 (7) 611-8.
Journal code: 7706787. ISSN: 0145-2126.

L11 ANSWER 12 OF 25 MEDLINE
TI Transcription abnormalities potentiate apoptosis of normal human fibroblasts.
SO MOLECULAR MEDICINE, (1997 Dec) 3 (12) 852-63.
Journal code: 9501023. ISSN: 1076-1551.

L11 ANSWER 13 OF 25 MEDLINE
TI Hypericin-induced apoptosis of human malignant glioma cells is light-dependent, independent of bcl-2 expression, and does not require
wild-type p53.
SO NEUROLOGICAL RESEARCH, (1997 Oct) 19 (5) 459-70.
Journal code: 7905298. ISSN: 0161-6412.

L11 ANSWER 14 OF 25 MEDLINE
TI Immunochemotherapy of malignant glioma: synergistic activity of CD95
ligand and **chemotherapeutics**.
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1997 Mar) 44 (1) 55-63.
Journal code: 8605732. ISSN: 0340-7004.

L11 ANSWER 15 OF 25 MEDLINE
TI Drug-induced apoptosis in hepatoma cells is mediated by the CD95 (APO-1/Fas) receptor/ligand system and involves activation of wild-type
p53.
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Feb 1) 99 (3) 403-13.
Journal code: 7802877. ISSN: 0021-9738.

L11 ANSWER 16 OF 25 MEDLINE
TI Apoptosis. Its significance in cancer and cancer therapy.
SO CANCER, (1994 Apr 15) 73 (8) 2013-26. Ref: 179
Journal code: 0374236. ISSN: 0008-543X.

L11 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI New insights into the kinetic resistance to anticancer agents.
SO Cytotechnology, (1998) Vol. 27, No. 1-3, pp. 225-235.
ISSN: 0920-9069.

L11 ANSWER 18 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI Potentiation of CD95L-induced apoptosis of human malignant glioma cells by
topotecan involves inhibition of RNA synthesis but not changes in CD95 or
CD95L protein expression.
SO Journal of Pharmacology and Experimental Therapeutics, (Sept., 1998) Vol.
386, No. 3, pp. 1374-1382.
ISSN: 0022-3565.

L11 ANSWER 19 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI p53 accumulation promotes dephosphorylation and proteolytic cleavage of
retinoblastoma protein in human malignant glioma cells.
SO Cellular Physiology and Biochemistry, (1997) Vol. 7, No. 6, pp. 304-311.
ISSN: 1015-8987.

L11 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI Genetic regulation and therapeutic modulation of apoptosis in human
malignant glioma.
SO Cellular Physiology and Biochemistry, (1996) Vol. 6, No. 6, pp. 376-380.
ISSN: 1015-8987.

L11 ANSWER 21 OF 25 CANCERLIT
TI 9-AMINOCAMPTOTHECIN INDUCES APOPTOSIS IN VITRO AND PROLONGS SURVIVAL OF
MICE WITH HUMAN RENAL CELL CARCINOMA XENOGRAFTS (Meeting abstract).
SO Proc Annu Meet Am Soc Clin Oncol, (1998) 17 A1284.

L11 ANSWER 22 OF 25 CANCERLIT
TI Immunologic cytotoxicity overcomes p53-mediated resistance to apoptosis
(Meeting abstract).

SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A3258.
ISSN: 0197-016X.

L11 ANSWER 23 OF 25 CANCERLIT
TI Expression of apoptotic genes in Pgp- and MRP-overexpressing tumor cells
(Meeting abstract).
SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A1924.
ISSN: 0197-016X.

L11 ANSWER 24 OF 25 CANCERLIT
TI Bcl-2 and chemoresistance in cancer (Meeting abstract).
SO Proc Annu Meet Am Assoc Cancer Res, (1995) 36 711.
ISSN: 0197-016X.

L11 ANSWER 25 OF 25 CANCERLIT
TI The bcl-2 gene family: expression and function (Meeting abstract).
SO Non-serial, (1994) 10th International Symposium on Cellular Endocrinology:
Molecular and Cell Biology of Apoptosis in Development, Disease and
Cancer, September 29-October 2, 1994, Lake Placid, NY, p. 43, 1994. .

=> D IBIB AB 17,16,15,14,8,6,5,1

L11 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:104527 BIOSIS
DOCUMENT NUMBER: PREV199900104527
TITLE: New insights into the kinetic resistance to anticancer agents.
AUTHOR(S): Chauffert, Bruno (1); Dimanche-Boitrel, Marie-Therese; Garrido, Carmen; Ivarsson, Mikael; Martin, Monique; Martin, Francois; Solary, Eric
CORPORATE SOURCE: (1) CJF INSERM 94/08, Fac. Med., 7 Bd Jeanne d'Arc, 21033 Dijon France
SOURCE: Cytotechnology, (1998) Vol. 27, No. 1-3, pp. 225-235.
ISSN: 0920-9069.
DOCUMENT TYPE: General Review
LANGUAGE: English
AB Kinetic resistance plays a major role in the failure of **chemotherapy** towards many solid tumors. Kinetic resistance to cytotoxic drugs can be reproduced in vitro by growing the cells as multicellular spheroids (Multicellular Resistance) or as hyperconfluent cultures (Confluence-Dependent Resistance). Recent findings on the cell cycle regulation have permitted a better understanding why cancer cells which arrest in long quiescent phases are poorly sensitive to cell-cycle specific anticancer drugs. Two cyclin-dependent kinase inhibitors (CDKI) seem particularly involved in the cell cycle arrest at the G1 to S transition checkpoint: the **p53**-dependent p21cip1 protein which is activated by DNA damage and the p27kip1 which is a mediator of the contact inhibition signal. Cell quiescence could alter drug-**induced** apoptosis which is partly dependent on an active progression in the cell cycle and which is facilitated by overexpression of oncogenes such as c-Myc or cyclins. Investigations are yet necessary to determine the influence of the cell cycle on the balance between antagonizing (bcl-2, bcl-XL...) or stimulating (Bax, Bcl-XS, **Fas** ...) factors in **chemotherapy-induced** apoptosis. Quiescent cells could also be protected from toxic agents by an enhanced **expression** of stress proteins, such as HSP27 which is **induced** by confluence. New strategies are required to circumvent kinetic resistance of solid tumors: adequate choice of anticancer agents whose activity is not altered by quiescence (radiation, cisplatin), recruitment from G1 to S/G2 phases by cell pretreatment with alkylating drugs or attenuation of CDKI activity by specific inhibitors.

L11 ANSWER 16 OF 25 MEDLINE
ACCESSION NUMBER: 94207957 MEDLINE
DOCUMENT NUMBER: 94207957 PubMed ID: 8156506
TITLE: Apoptosis. Its significance in cancer and cancer therapy.
COMMENT: Erratum in: Cancer 1994 Jun 15;73(12):3108
AUTHOR: Kerr J F; Winterford C M; Harmon B V
CORPORATE SOURCE: Department of Pathology, University of Queensland Medical School, Herston, Australia.
SOURCE: CANCER, (1994 Apr 15) 73 (8) 2013-26. Ref: 179
Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199405
ENTRY DATE: Entered STN: 19940526
Last Updated on STN: 19950206
Entered Medline: 19940518
AB Apoptosis is a distinct mode of cell death that is responsible for deletion of cells in normal tissues; it also occurs in specific pathologic contexts. Morphologically, it involves rapid condensation and budding of the cell, with the formation of membrane-enclosed apoptotic bodies containing well-preserved organelles, which are phagocytosed and digested by nearby resident cells. There is no associated inflammation. A characteristic biochemical feature of the process is double-strand cleavage of nuclear DNA at the linker regions between nucleosomes leading to the production of oligonucleosomal fragments. In many, although not all of the circumstances in which apoptosis occurs, it is suppressed by inhibitors of messenger RNA and protein synthesis. Apoptosis occurs spontaneously in malignant tumors, often markedly retarding their growth, and it is **increased** in tumors responding to irradiation, cytotoxic **chemotherapy**, heating and hormone ablation. However, much of the current interest in the process stems from the discovery that it can be regulated by certain proto-oncogenes and the **p53** tumor suppressor gene. Thus, c-myc **expression** has been shown to be involved in the initiation of apoptosis in some situations, and bcl-2 has emerged as a new type of proto-oncogene that inhibits apoptosis, rather than stimulating mitosis. In **p53**-negative tumor-derived cell lines transfected with wild-type **p53**, **induction** of the gene has, in rare cases, been found to cause extensive apoptosis, instead of growth arrest. Finally, the demonstration that antibodies against a cell-surface protein designated **APO-1** or **Fas** can enhance apoptosis in some human lymphoid cell lines may have therapeutic implications.

L11 ANSWER 15 OF 25 MEDLINE
ACCESSION NUMBER: 97174339 MEDLINE
DOCUMENT NUMBER: 97174339 PubMed ID: 9022073
TITLE: Drug-induced apoptosis in hepatoma cells is mediated by the CD95 (APO-1/Fas) receptor/ligand system and involves

activation of wild-type p53.
AUTHOR: Muller M; Strand S; Hug H; Heinemann E M; Walczak H;
Hofmann W J; Stremmel W; Krammer P H; Galle P R
CORPORATE SOURCE: University Hospital, Department of Internal Medicine IV,
Heidelberg, Germany.
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1997 Feb 1) 99 (3)
403-13.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970321
Last Updated on STN: 19970321
Entered Medline: 19970310

AB **Chemotherapeutic** drugs are cytotoxic by **induction** of apoptosis in drug-sensitive cells. We investigated the mechanism of bleomycin-**induced** cytotoxicity in hepatoma cells. At concentrations present in the sera of patients during therapy, bleomycin **induced** transient accumulation of nuclear wild-type (wt) **p53** and upregulated **expression** of cell surface **CD95 (APO-1/Fas)** receptor in hepatoma cells carrying wt **p53** (HepG2). Bleomycin did not **increase CD95** in hepatoma cells with mutated **p53** (Huh7) or in hepatoma cells which were **p53**-/- (Hep3B). In addition, sensitivity towards **CD95**-mediated apoptosis was also **increased** in wt **p53** positive HepG2 cells. Microinjection of wt **p53** cDNA into HepG2 cells had the same effect. In contrast, bleomycin did not enhance susceptibility towards **CD95** -mediated apoptosis in Huh7 and in Hep3B cells. Furthermore, bleomycin treatment of HepG2 cells **increased CD95** ligand (CD95L) mRNA **expression**. Most notably, bleomycin-**induced** apoptosis in HepG2 cells was almost completely inhibited by antibodies which interfere with **CD95** receptor/ligand interaction. These data suggest that apoptosis **induced** by bleomycin is mediated, at least in part, by **p53**-dependent stimulation of the **CD95** receptor/ligand system. The same applies to other anti-cancer drugs such as cisplatin and methotrexate. These data may have major consequences for drug treatment of cancer and the explanation of drug sensitivity and resistance.

L11 ANSWER 14 OF 25 MEDLINE
ACCESSION NUMBER: 97265679 MEDLINE
DOCUMENT NUMBER: 97265679 PubMed ID: 9111585
TITLE: Immunochemotherapy of malignant glioma: synergistic activity of CD95 ligand and **chemotherapeutics**.
AUTHOR: Roth W; Fontana A; Trepel M; Reed J C; Dichgans J; Weller M
CORPORATE SOURCE: Department of Neurology, University of Tubingen, School of Medicine, Germany.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1997 Mar) 44 (1) 55-63.
Journal code: 8605732. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 19970523
Last Updated on STN: 19970523
Entered Medline: 19970509

AB Malignant glioma cells are susceptible to **CD95(Fas** /APO-)-mediated apoptosis triggered by agonistic antibody. Here we examined the proapoptotic effects of the natural **CD95** ligand, a cytotoxic cytokine homologous to tumor necrosis factor, on malignant glioma cell lines LN-229, LN-308 and T98G. We assessed whether glioma cell killing is synergistically enhanced by cotreatment with **CD95** ligand and **chemotherapeutic** agents, including doxorubicin, carmustine, vincristine, etoposide, teniposide, 5-fluorouracil and cytarabine. Synergy was examined at low concentrations of cytotoxic drugs and **CD95** ligand with a defined effect level (IC15). Short-term-cytotoxicity assays showed prominent killing of the glioma cells by **CD95** ligand but not by the drugs at relevant concentrations. **CD95** ligand **induced** apoptosis in the acute toxicity paradigm was augmented by doxorubicin and vincristine. Growth-inhibition assays revealed prominent synergy between **CD95** ligand and all drugs examined. The best synergy was obtained with **CD95** ligand and doxorubicin, vincristine or teniposide. The strong synergistic antiproliferative effects were observed at much lower concentrations of **CD95** ligand and cytotoxic drugs than the moderate synergistic acute cytotoxic effects. All cell lines examined **express** the Bcl-2 protein. LN-229 has partial wild-type **p53** activity. T98G has mutant **p53**, LN-308 has a deleted **p53** gene and lacks **p53** protein **expression**. Thus, synergistic effects of **CD95** ligand and cytotoxic drugs were observed in cell lines exhibiting two features thought to play a role in the chemoresistance of human malignant glioma cells: loss of wild-type **p53** activity and acquisition of bcl-2 **expression**. Ectopic **expression** of murine bcl-2 conferred partial protection from **CD95** ligand and drugs when administered alone but did not interfere with the mechanisms underlying the synergistic effects of **CD95** ligand and **chemotherapeutic** drugs.

L11 ANSWER 8 OF 25 MEDLINE
ACCESSION NUMBER: 1998416586 MEDLINE
DOCUMENT NUMBER: 98416586 PubMed ID: 9743944
TITLE: Molecular determinants of apoptosis induced by cytotoxic drugs.
AUTHOR: Fulda S; Friesen C; Debatin K M
CORPORATE SOURCE: University Children's Hospital, Ulm, Germany.
SOURCE: KLINISCHE PADIATRIE, (1998 Jul-Aug) 210 (4) 148-52.
Journal code: 0326144. ISSN: 0300-8630.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981216

AB Recent experimental evidence suggests that apoptosis pathways such as the **CD95** system are an important mediator of **chemotherapy-induced** apoptosis in various tumor cell lines. Therapeutic concentrations of cytotoxic drugs **induce CD95** and **CD95**-L that mediates apoptosis via an autocrine/paracrine loop by crosslinking **CD95**. Interfering with **CD95**-L/receptor interaction by antagonistic antibodies to the receptor or by inhibition of **CD95**-L **expression** strongly reduces apoptosis. Drug-**induced** apoptosis critically depends on activation of caspases since apoptosis is almost completely abrogated by the caspase inhibitor zVAD-fmk. The receptor apical caspase FLICE/MACH (caspase-8) and the downstream caspase CPP32 (caspase-3) are cleaved resulting in processing

of substrates such as the nuclear enzyme PARP. In addition, the response
to cytotoxic drugs is modulated by pro- and antiapoptotic proteins of the
Bcl-2 family and **p53**. Defects in apoptosis pathways, e.g. deficient upregulation of **CD95**-L, downregulation of **CD95 expression** or blockade of caspase activation may confer resistance to cytotoxic drug treatment. Thus, chemosensitivity of tumor cells depends
on intact apoptosis pathways such as the **CD95** system that are activated by **chemotherapeutic** drugs. These findings may have implications for drug sensitivity and resistance of tumor cells.

L11 ANSWER 6 OF 25 MEDLINE
ACCESSION NUMBER: 1999059827 MEDLINE
DOCUMENT NUMBER: 99059827 PubMed ID: 9841917
TITLE: p53 activates the CD95 (APO-1/Fas) gene in response to DNA
damage by anticancer drugs.
AUTHOR: Muller M; Wilder S; Bannasch D; Israeli D; Lehlbach K;
Li-Weber M; Friedman S L; Galle P R; Stremmel W; Oren M;
Krammer P H
CORPORATE SOURCE: Department of Internal Medicine IV, Hepatology and
Gastroenterology, University Hospital, 69115 Heidelberg, Germany.
CONTRACT NUMBER: DK373402 (NIDDK)
RO1 CA 40099 (NCI)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Dec 7) 188 (11)
2033-45.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ011034
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990202
Last Updated on STN: 20000303
Entered Medline: 19990120

AB **Chemotherapeutic** drugs cause DNA damage and kill cancer cells mainly by apoptosis. **p53** mediates apoptosis after DNA damage. To explore the pathway of **p53**-dependent cell death, we investigated if **p53**-dependent apoptosis after DNA damage is mediated by the **CD95** (**APO-1/Fas**) receptor/ligand
system. We investigated hepatoma, gastric cancer, colon cancer, and breast
cancer cell lines upon treatment with different anticancer agents known to
act via **p53** accumulation. Cisplatin, mitomycin, methotrexate, mitoxantrone, doxorubicin, and bleomycin at concentrations present in the
sera of patients during therapy led to an upregulation of both **CD95** receptor and **CD95** ligand. **Induction** of
the **CD95** ligand occurred in **p53** wild-type (wt), **p53** mutant (mt), and **p53** deficient (**p53**(-/-)) cell lines and at wt and mt conformation of temperature-sensitive **p53** mutants. In contrast, upregulation of the **CD95** receptor was observed only in cells with wt **p53**, not in cells with mt or without any **p53**. Restitution of **inducible** wt **p53** function restored the ability of **p53**(-/-) Hep3B cells to upregulate the **CD95** receptor in response to anticancer drugs. This rendered the cells sensitive to **CD95**-mediated apoptosis. In an attempt to understand how **CD95 expression** is regulated by **p53**, we identified a **p53**-responsive element within the first intron of the **CD95** gene, as well as three putative elements within the promoter. The intronic
element conferred transcriptional activation by **p53** and cooperated with **p53**-responsive elements in the promoter of the **CD95** gene. wt **p53** bound to and transactivated the **CD95** gene, whereas mt **p53** failed to **induce** apoptosis via activation of the **CD95** gene. These observations provide a mechanistic explanation for the ability of **p53** to contribute to tumor progression and to resistance of cancer cells to **chemotherapy**.

L11 ANSWER 5 OF 25 MEDLINE
ACCESSION NUMBER: 1999218643 MEDLINE
DOCUMENT NUMBER: 99218643 PubMed ID: 10200532
TITLE: The CD95/CD95 ligand system is not the major effector in
anticancer drug-mediated apoptosis.
AUTHOR: Tolomeo M; Dusonchet L; Meli M; Grimaudo S; D'Alessandro N;
Papoff G; Ruberti G; Rausa L
CORPORATE SOURCE: Chair of Hematology, University of Palermo, Italy.
SOURCE: CELL DEATH AND DIFFERENTIATION, (1998 Sep) 5 (9) 735-42.
Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990614
Last Updated on STN: 19990614
Entered Medline: 19990528

AB Many anticancer drugs are able to **induce** apoptosis in tumor cells but the mechanisms underlying this phenomenon are poorly understood.
Some authors reported that the **p53** tumor suppressor gene may be responsible for drug-**induced** apoptosis; however, **chemotherapy-induced** apoptosis can also be observed in **p53** negative cells. Recently, doxorubicin (DXR) was reported to **induce** CD95L **expression** to mediate apoptosis through the **CD95**/CD95L system. Thus, an impairment of such a system may be involved in drug resistance. We evaluated the in vitro antitumor activity
of several cytotoxic drugs on two human **p53**-negative T-cell lymphoma cell lines, the HUT78-B1 CD95L-resistant cell line and the HUT78
parental CD95L-sensitive cell line. We demostrated by Western blotting
assay that DXR and etoposide (VP-16) were able to **induce** CD95L **expression** after 4 h of treatment. In contrast, they were unable to **induce** the **expression** of **p53**. DXR, at
concentrations ranging from 0.001 - 1 &mgr;g/ml, and VP16, at
concentrations ranging from 0.05 - 1 &mgr;g/ml, were equally cytotoxic and
induced apoptosis in both cell lines as assessed by fluorescence microscopy and flow cytometry analyses. Although we observed a slightly
reduced percentage of apoptotic cells in HUT78B1 when compared with the
parental HUT78 cells after few hours of drug exposure, this difference was
no longer evident at 48 or 72 h. Similarly, the exposure of HUT78 cells to
a **CD95**-blocking antibody partially reduced early apoptosis (24 h) without affecting the long-term effects of the drugs including
cytotoxicity. Furthermore, as observed with DXR and VP-16, both the
CD95L-sensitive and the CD95L-resistant cell lines resulted equally sensitive to the cytotoxic effects of a number of different cytotoxic drugs (vincristine, camptothecin, 5-fluorouracil and methotrexate). The
treatment with the Caspase-3 tetrapeptide aldehyde inhibitor, Ac-DEVD-CHO,
did not affect the DXR-**induced** apoptosis whereas it only modestly inhibited apoptosis and cytotoxicity of VP-16, while Z-VAD.FMK, a
Caspase inhibitor that prevents the processing of Caspase-3 to its active

form, was able to block DXR-**induced** apoptosis at 24 h but not at 48 h. Thus, our results do not confirm a crucial role for the **CD95** /CD95L system in drug-**induced** apoptosis and suggest the involvement of alternative **p53**-independent pathways at least in this experimental model system.

L11 ANSWER 1 OF 25 MEDLINE
ACCESSION NUMBER: 1999304009 MEDLINE
DOCUMENT NUMBER: 99304009 PubMed ID: 10200578
TITLE: p53-mediated up-regulation of CD95 is not involved in genotoxic drug-induced apoptosis of human breast tumor cells.
AUTHOR: Ruiz-Ruiz M C; Lopez-Rivas A
CORPORATE SOURCE: Instituto de Parasitologia y Biomedicina, CSIC, calle Ventanilla 11, 18001 Granada, Spain.
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AB **Induction** of **CD95** (**Fas/APO-1**) and **CD95** ligand during **chemotherapeutic** treatment may contribute to the death by apoptosis of some tumor cells. In this study, we have analyzed the role of the **CD95** system in genotoxic drug-**induced** death of human breast tumor cells. Incubation of the breast tumor cell lines MCF-7 and EVSA-T with doxorubicin or methotrexate caused apoptosis after 48 h of treatment. These drugs **induced** a marked **increase** in the level of **CD95** mRNA and protein in wild-type **p53-expressing** MCF-7 cells. On the contrary, the breast cancer cell line EVSA-T that **expresses** high levels of an inactive form of **p53**, did not up-regulate **CD95** upon drug treatment. Elevation of **CD95 expression** by DNA-damaging drugs was notably blocked in MCF-7 cells **expressing** the human papillomavirus type 16 E6 protein (E6 cells) which prevented **p53** accumulation upon DNA damage. However, E6 cells were still killed by the drugs. Furthermore, the genotoxic drugs did not **induce** the **expression** of **CD95** ligand in MCF-7 cells at doses that caused apoptosis in these breast tumor cells. Moreover, drug-**induced** apoptosis of breast tumor cells was not prevented in the presence of either a **CD95** antagonistic antibody or a **CD95** ligand blocking antibody. We also observed a strong synergism between lower doses of DNA-damaging drugs and **CD95** agonistic antibody in the **induction** of apoptosis in MCF-7 cells. In summary, our data indicate that drug-**induced** apoptosis of breast tumor cells occurs by a **CD95**/CD95L-independent mechanism although by elevating the tumor suppressor proteins **p53** and **CD95**, genotoxic drugs may sensitize breast tumor cells to **CD95**-mediated apoptosis.

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FILE 'MEDLINE, BIOSIS, CAPLUS, CANCERLIT' ENTERED AT 09:54:18 ON 02 SEP 2002
L1 37622 S CD95 OR FAS OR APO-1
L2 10247137 S INCREAS? OR INDUC?
L3 22697 S L1(S)L2
L4 2705546 S EXPRESS?
L5 13033 S L3(S)L4
L6 104368 S P53
L7 953 S L5(S)L6
L8 439321 S CHEMOTHERAP?
L9 112 S L7 AND L8
L10 46 DUP REM L9 (66 DUPLICATES REMOVED)
L11 25 S L10 NOT PY>1999

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